REMARKS

Applicants amend claims 1, 4-6, 9, 15, 21-23, 25, 26 and 29-36. No new claims have been added, therefore claims 1-6, 9,10,15, and 21-36 are pending.

Abstract

The Examiner maintains his objection to the Abstract of the Disclosure because the previous amendment was not submitted on a separate sheet as required by 37 CFR § 1.72(b). Applicants include an amended version of the abstract herewith as well on an attached separate sheet marked "Substitute Version of the Abstract."

Information Disclosure Statement

The Examiner acknowledges receipt of the English translation of French patent FR 2.168.137(72.01439), but indicates that no Information Disclosure Statement (PTO Form 1449) was filed. Applicants include a Supplemental IDS on the attached PTO Form 1449 which lists this representative French patent. The complete English translation of FR 2.168.137 is representative of the five French patents listed on page 7, lines 28-33 of the original specification. Applicants believe that the provision of the full translation of the representative French patent on the enclosed PTO Form 1449 fulfills the requirements of MPEP § 609(A)(3).

Rejection of Claims under 35 U.S.C. § 112

Claims 1-6, 9, 10 and 15 are rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their

invention. In response to the Examiner's concerns, Applicants have amended these claims as described below.

Claim 1 is objected to for omitting essential elements, such omission amounting to a gap between the elements. Particularly, the Examiner indicates that claim 1 fails to positively and distinctly define the invention. Claim 1 has been amended to recite that the compound first binds to and then enhances the clearing of the cholesterol containing low-density lipoprotein after subsequent binding to the low-density lipoprotein receptor. Claim 1, step (c) has been clarified to recite that the binding of the compound to the cholesterol containing low-density lipoprotein forms a complex.

Claim 4 has been amended to clarify that the compound binds to the cholesterol low-density lipoprotein and that the binding is assessed by a sandwich immunoreactivity assay.

Claim 5 has been amended to correct the lack of antecedent support in reciting "the binding". Claim 5 has also been amended to clarify that the compound binds to a cholesterol containing low-density lipoprotein and forms a complex.

Claim 6 has been amended to clarify that the compound first binds to and then increases the clearance of a low density lipoprotein after subsequent binding to the low-density lipoprotein receptor. Claim 6, step (ii) has also been amended to clarify that the compound binds to the low-density lipoprotein and forms a complex. The lack of antecedent support of step (iii) is corrected as well.

Claim 9 has been amended to clarify that an epitope on the apolipoprotein B-100 binds to an LDL receptor. Claim 9, step (i) has been amended to indicate that the compound is mixed

with low-density lipoprotein and allowed to bind to it. Claim 9 was also clarified to more accurately recite the sandwich immunoreactivity assay.

Claim 15 has been amended to clarify the that the compound first binds to a lipoprotein and enhances the binding of the lipoprotein to a low-density lipoprotein hepatic receptor.

Claim 21 has been amended to correct the dependency from claim 1 to claim 2.

Claim 22 has been amended to clarify that the lipoprotein receptor is hepatic.

Claim 23 has been amended to omit the words "cholesterol containing."

Claims 25 and 26 have been amended to clarify that the compound binds to the low-density lipoprotein and forms a complex.

Claims 29, 33 and 34 have been amended to correct their dependency from claim 10 to claim 9.

Claim 30 has been amended to clarify that the cholesterol containing lipoprotein is a low-density with lipoprotein.

Claims 31 and 32 have been amended to correct the antecedent basis of the word "binding".

Claims 35 and 36 have been amended to incorporate the words "low-density" before lipoprotein.

Prior Art Rejections

The amended claims are directed to a method to determine whether a compound will increase the clearance of a low density lipoprotein in a host, that includes mixing the compound with low density lipoprotein; determining whether the compound and the low density lipoprotein

form a complex; and determining whether the complex alters the three dimensional conformation of the lipoprotein such that the binding of the lipoprotein to a lipoprotein receptor is enhanced. As stated on pages 13-14 of the application, prior to this discovery, it was not known that one could lower serum cholesterol by administering a compound that intercalates into cholesterol-bearing LDL in a manner that increases binding efficiency to clearing receptors. **Since the present claims are assay claims based on this novel mechanism of action, they can not be rendered obvious by the prior use or disclosure of compounds to lower cholesterol that either act through unrelated mechanisms or which act through unknown mechanisms, neither of which would teach the public to carry out the present assay.**

Rejection of Original Claims 1-3, 6 21-24 and 28 Under 35 U.S.C. § 102 (b) as Anticipated by Mao *et al.* (WO95/15760)

Mao *et al.* discloses administering certain 2,6-di-alkyl-4-silyl-phenols including those synthesized on pages 7-14 to lower cholesterol levels in patients with hypercholesterolemia. Mao does not address the mechanism of action of these compounds, and therefore, could not disclose or render obvious a screen based on discovery of a mechanism of action. Mao does not, in fact, disclose any screening procedures, because the Mao invention is based on a identification of a class of compounds to lower cholesterol through an unknown or undescribed pathway.

The Examiner contends that the compounds disclosed by Mao *et al* would have inherently caused a conformational change in LDL so as to bind an LDL receptor and thus enhance the clearance of cholesterol-containing LDL from the plasma. The Applicants respond, with respect, that notwithstanding the fact that there is no evidence of record how the Mao compounds work, the Examiner's point even if correct is irrelevant to the pending claims. The

Examiner is focused on an inherency argument relevant to a **method of treatment** claim. The current application is directed to *methods of assessing* the ability of a compound to enhance LDL clearance. In assessing the obviousness of the present **screening** claims, the Examiner must look to prior screening claims that teach the identification of a compound based on its ability to form a complex with the lipoprotein, and then determining whether the newly formed complex causes a change in the structure of apoB-100 that results in increased binding affinity to an LDL receptorinteract with apo-B- 1, or a prior disclosure of this mechanism. Mao provides neither.

Rejection of Original Claims 1-3, 6, 21-24 and 28 Under 35 U.S.C. § 102(b) as Anticipated by Grundy (Oates [sic]) (New England Journal of Medicine 319:24-33, 1988)

The Examiner suggests that claims 1-3, 6, 21-24 and 28 are inherently anticipated under 35 U.S.C. § 102(b) by Grundy. The Examiner states that Grundy teaches that compounds such as mevastatin, compactin and lovastatin can be classified as inhibitors of HMG-CoA reductase and lower cholesterol and LDL levels in patients thus qualifying them as LDL-clearance enhancing drugs. The Examiner then makes a leap in logic by stating on page 9 of the Office Action that the drugs disclosed in Grundy "would have inherently caused LDL to change in conformation so as to bind an LDL receptor to enhance clearance of cholesterol-containing LDL from peripheral tissues." There is no evidence of record supporting the Examiner's position. This is an inaccurate characterization of the mechanism of the drugs disclosed in Grundy.

Grundy on its face teaches that the disclosed compounds act through a different mechanism than that which is the basis of the claimed screen. In particular, Grundy teaches that the compounds are 3-hydroxy-3-methylglutaryl coenzyme A (i.e., HMG-CoA) reductase

inhibitors. By inhibiting the key enzyme in cholesterol biosynthesis, these drugs act to decrease the cellular levels of cholesterol. As a consequence of this action, as stated on page 26, column 1, paragraph 1, these drugs **"increase the expression of LDL receptors."** As discussed in the subsequent paragraph, the consequence of increasing the **number** of LDL receptors is to enhance the clearance of cholesterol from the body.

In contrast, the present screen selects for compounds which effectively **intercalate into cholesterol-bearing lipoprotein**. Thus the compounds screened for in the present invention actually physically bind to the lipoprotein. The reductase inhibitors of Grundy **do not** act by binding to the lipoprotein and hence would not be assumed to affect the three-dimensional conformation of the receptor. These two mechanisms are completely unrelated. No person of ordinary skill would be taught to carry out the present screen, or even be motivated to try the present screen, by the disclosure of HMG-CoA reductase inhibitor compounds which **do not** act by intercalating into cholesterol-bearing lipoproteins. Moreover, because the present screen selects for compounds which act via a distinct mechanism than reductase inhibitors, it would be inaccurate to conclude that the compounds disclosed in Grundy could inherently cause a change in the LDL receptor without presentation of any supporting evidence.

Rejection of claims 4-5, 9, 10, 15, 25-27, 29-36 Under 35 U.S.C. § 103(a) as Obvious Over Mao *et al.* or Grundy *et al.* in view of Koren *et al.*

The Examiner rejects claims 4-5, 9, 10, 15, 25-27, 29-36 under 35 U.S.C. § 103(a) as unpatentable over over Mao *et al.* or Grundy *et al.* in view of Koren *et al.* The Examiner states that although Mao and Grundy differ in failing to teach quantifying lipoproteins and apolipoproteins using sandwich immunoassay or agarose electrophoresis, Koren discloses

quantifying immunoreactive concentrations of lipoprotein and apolipoprotein including apo B-100 (LDL and VLDL) using sandwich immunoreactivity assays wherein antibodies specific to apo B-100 are immobilized into microwells as capture antibodies and labeled as secondary antibodies to capture and quantify the LDL concentration respectively. The Examiner also states that one of ordinary skill in the art at the time the invention was made would have been motivated to use the sandwich immunoassay or agarose electrophoresis as disclosed by Koren *et al.* to detect binding for the screening of compounds such as in the methods taught by Mao or Grundy. In particular, the Examiner states that Koren discloses assays which provide antibodies specific for epitopes allowing for the quantification of LDL, VLDL or apo B-100 for use in determining accurate antigenic levels in serum and plasma.

Applicants respectfully traverse this rejection. As the Examiner is aware, to establish a *prima facie* case of obviousness, the following criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation or success; and (3) the combined references must teach or suggest all the claim limitations. The teaching or suggestion must be found in the prior art and not in the applicant's disclosure. The references cited by the Examiner do not provide any suggestion or motivation that they can be combined in the manner described in the Office Action. Furthermore, the combined references do not teach or suggest all the claim limitations.

One of ordinary skill in the art would not have been motivated to combine the compounds disclosed in Mao with the assays of Koren to invent the current screening methods

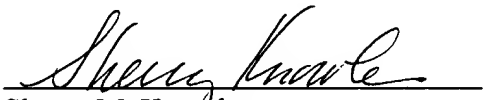
because Mao provides no teaching or suggestion of the mechanism by which his drugs operate to lower cholesterol levels. Thus, one skilled would not have had any reasonable expectation of success to produce a screen for compounds that function to lower cholesterol levels by binding to the cholesterol-containing lipoprotein. By similar reasoning, one skilled in the art would not have considered combining the compounds disclosed in Grundy with the assays of Koren because again, those compounds disclosed in the Grundy reference act through a **completely different mechanism** than do the compounds screened for with the present invention.

The Examiner provides no evidence as to how one so skilled could have been motivated to combine these references in the manner in which the Office Action suggests. Thus, Applicants contend that the Examiner has not met his burden of establishing a *prima facie* case of obviousness, because there is (1) **no** suggestion or motivation to modify the references or to combine the reference teachings; (2) **no** reasonable expectation of success; and (3) the combined references **do not** teach or suggest all the claim limitations.

CONCLUSION

Based on the above-presented amendments and comments, Applicants request that the Examiner allow all pending claims.

Respectfully submitted,



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MARKED-UP VERSION OF THE CLAIM AMENDMENTS

1. (Twice Amended) A method to assess whether a compound first binds to and then enhances the clearing of a cholesterol-containing low density lipoprotein **(LDL) after subsequent binding to the low density lipoprotein receptor** in a host human or other animal comprising:

(a) administering the compound to the host;

(b) isolating **the** cholesterol-containing low density lipoprotein from the host,

(c) determining whether the **binding of the** compound [~~has bound~~] to the cholesterol-containing **low density** lipoprotein [~~to form~~] **forms** a complex; and

(d) determining whether the complex results in a change in the three dimensional conformation of the lipoprotein that enhances the binding affinity of the lipoprotein to the [~~LDL~~] **low density lipoprotein** receptor.

4. (Amended) The method of claim 1, wherein the binding of the compound to the **cholesterol-containing low density lipoprotein** [~~complex~~] is assessed by a sandwich immunoreactivity assay.

5. (Amended) The method of claim 1, wherein the binding of the compound to the **cholesterol-containing low density lipoprotein** [~~complex~~] is assessed using agarose electrophoresis.

6. (Twice Amended) A method to determine whether a compound first binds to and then increases [~~will increase~~] the clearance of a low density lipoprotein **after subsequent binding to the low density lipoprotein receptor** in a host, comprising

(i) mixing the compound with low density lipoprotein;

(ii) determining whether the compound **binds to** [~~and~~] the low density lipoprotein **and forms** [~~form~~] a complex; and

(iii)determining whether the complex alters the three dimensional conformation of the lipoprotein such that the binding of the lipoprotein to a lipoprotein receptor is enhanced.

9. (Twice Amended) A method to determine if a compound causes a change in the structure of apolipoprotein B-100 in a cholesterol-containing low density lipoprotein, **wherein, an epitope on the apolipoprotein B-100 binds to an LDL-receptor,** [~~that would be therapeutically useful~~], comprising:

(i) mixing the compound with **and allowing it to bind to** low density lipoprotein;

(ii) carrying out a sandwich immunoreactivity assay on the **compound-low** density lipoprotein mixture using [~~an~~] **a first** antibody directed to the epitope on apolipoprotein B-100 that binds to the LDL-receptor,

(iii) using a second, **capture** antibody **that is attached to a solid phase and which binds to the first antibody;** [~~to quantify the amount of LDL captured by the assay; and~~]

(iv) detecting the second capture antibody bound to the first antibody

(v) quantifying the amount of the first antibody - LDL - compound captured by the second antibody; and

[~~(iv)~~]**(vi)** comparing the amount of LDL captured by the assay to a control.

15. (Twice Amended) A method for assessing whether a compound **first binds to a lipoprotein,** [~~enhances~~] **enhancing** the binding of the lipoprotein to a **low density** lipoprotein **hepatic** receptor and thus [~~lowers~~] **lowering** plasma cholesterol, the method comprising:

(a) allowing the compound to form a complex with a cholesterol-containing lipoprotein in vivo,

(b) isolating the resulting complex, and

(c) determining whether the formation of the complex causes a change in the three dimensional conformation of apoB-100 in the lipoprotein that enhances the binding of the lipoprotein to the LDL hepatic receptor.

21. (Amended) The method of claim [~~1~~]**2**, wherein the apolipoprotein is apoB-100.

22. (Amended) The method of claim 1, wherein the lipoprotein receptor is [~~the low density lipoprotein~~] hepatic [~~receptor~~].

23. (Amended) The method of claim 6, wherein the [~~cholesterol-containing~~] lipoprotein is VLDL.

25. (Amended) The method of claim 6, wherein the **determination of whether** [~~binding of~~] the compound **binds** to the **low-density lipoprotein and forms a complex** [~~complex~~] is assessed by a sandwich immunoreactivity assay.

26. (Amended) The method of claim 6, wherein the **determination of whether** [~~binding of~~] the compound **binds** to the **low-density lipoprotein and forms a complex** [~~complex~~] is assessed using agarose electrophoresis.

29. (Amended) The method of claim [~~10~~] **9**, wherein the control is cholesterol-containing low density lipoprotein in the absence of test compound.

30. (Amended) The method of claim 10, wherein the cholesterol-containing **low-density** lipoprotein is VLDL.

31. (Amended) The method of claim 15, wherein the **formation of** [~~binding of the compound to~~] the complex is determined by a sandwich immunoreactivity assay.

32. (Amended) The method of claim 15, wherein the **formation of** [~~binding of the compound to~~] the complex is determined using agarose electrophoresis.

33. (Amended) The method of claim [~~10~~] **9**, wherein the apolipoprotein is apoB-100.

34. (Amended) The method of claim [~~10~~] **9**, wherein the lipoprotein receptor is [~~the~~] **a** low density lipoprotein (LDL) receptor.

35. (Amended) The method of claim 15, wherein the cholesterol-containing **low-density** lipoprotein is LDL.

36. (Amended) The method of claim 15, wherein the cholesterol-containing **low-density** lipoprotein is VLDL.